

García-Carbonero R, Mayordomo JI, et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: A multicenter randomized trial. J Natl Cancer Inst. 2001;3:31-38. Febrile neutropenia is sometimes referred to as an “oncologic emergency.” Indeed, it can carry significant morbidity and mortality, and certainly constitutes a large portion of our inpatient admissions here at CPMC. While the role of early antibiotics is well-established and crucial, adjunctive therapies including hematopoietic colony stimulating factors are more controversial. The current study aims to address this controversy. As febrile neutropenic patients are not a homogeneous group (e.g., there is a preponderance of data suggesting that low-risk patients should be treated in an outpatient setting), this study focused on the high risk category (risk factors including sepsis & poor performance status). In this multicenter randomized trial of 210 patients, the authors show that the addition of G-CSF to an antibiotic regimen for patients with fever and neutropenia leads not only to shorter duration of neutropenia, but also to reduced hospital stay and possibly to reduced costs as well. This is a very limited study however - it was open-label, unblinded, and not placebo-controlled. Patients with leukemia & those undergoing myeloablative chemotherapy were excluded as well. Mortality was similar in both the control and experimental group. Nonetheless, the study does provide support for the administration of G-CSF to high-risk solid tumor patients with fever and neutropenia. For a good Cochrane review on this literature, see Journal of Clinical Oncology 2005;23:4198-4214.

Granulocyte Colony-Stimulating Factor in the Treatment of High-Risk Febrile Neutropenia: a Multicenter Randomized Trial

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Background: Granulocyte colony-stimulating factors (G-CSFs) have been shown to help prevent febrile neutropenia in certain subgroups of cancer patients undergoing chemotherapy, but their role in treating febrile neutropenia is controversial. The purpose of our study was to evaluate—in a prospective multicenter randomized clinical trial—the efficacy of adding G-CSF to broad-spectrum antibiotic treatment of patients with solid tumors and high-risk febrile neutropenia. **Methods:** A total of 210 patients with solid tumors treated with conventional-dose chemotherapy who presented with fever and grade IV neutropenia were considered to be eligible for the trial. They met at least one of the following high-risk criteria: profound neutropenia (absolute neutrophil count $<100/\text{mm}^3$), short latency from previous chemotherapy cycle (<10 days), sepsis or clinically documented infection at presentation, severe comorbidity, performance status of 3–4 (Eastern Cooperative Oncology Group scale), or prior inpatient status. Eligible patients were randomly assigned to receive the antibiotics ceftazidime and amikacin, with or without G-CSF (5 $\mu\text{g}/\text{kg}$ per day). The primary study end point was the duration of hospitalization. All *P* values were two-sided. **Results:** Patients randomly assigned to receive G-CSF had a significantly shorter duration of grade IV neutropenia (median, 2 days versus 3 days; $P = .0004$), antibiotic therapy (median, 5 days versus 6 days; $P = .013$), and hospital stay (median, 5 days versus 7 days; $P = .015$) than patients in the control arm. The incidence of serious medical complications not present at the initial clinical evaluation was 10% in the G-CSF group and 17% in the control group ($P = .12$), including five deaths in each study arm. The median cost of hospital stay and the median overall cost per patient admission were reduced by 17% ($P = .01$) and by 11% ($P = .07$), respectively, in the G-CSF arm compared with the control arm. **Conclusions:** Adding G-CSF to antibiotic therapy shortens the duration of neutropenia, reduces the duration of antibiotic therapy and hospitalization, and decreases hospital costs in patients with high-risk febrile neutropenia. [J Natl Cancer Inst 2001;93:31–8]

The association of neutropenia and infection continues to be a major cause of morbidity and mortality in cancer patients receiving myelosuppressive chemotherapy (1). Prompt initiation of empiric broad-spectrum antibiotics has effectively improved the outcome of patients with febrile neutropenia. However, a substantial proportion of these patients require prolonged hospital stays or develop more severe medical complications. Both the degree and the duration of neutropenia are key factors closely related to the risk and outcome of infection (2).

Hematopoietic colony-stimulating factors (CSFs), such as granulocyte CSF (G-CSF) and granulocyte–macrophage CSF, have been shown to promote proliferation, differentiation, and function of progenitor and mature cells of the myeloid lineage (3). These cytokines also stimulate the bactericidal functions of mature neutrophils (4). When administered as a preventive adjunct to chemotherapy, CSFs have shown in clinical trials to shorten the neutropenic period and to reduce by 50% the incidence of febrile neutropenia in high-risk patients (5,6). However, the role of CSFs in the treatment of febrile neutropenia remains uncertain, despite several randomized studies that have attempted to address this issue (7–12).

Patients with fever and neutropenia are not a homogeneous group, and not all such patients have the same risk of developing infections or serious complications or of dying during a febrile episode. Talcott et al. (13,14) developed a risk-assessment model for episode outcome by use of clinical variables that could be assessed within 24 hours of presentation with fever and neutropenia. Patients with risk factors, including prior inpatient status, serious independent comorbidity, or uncontrolled cancer, had a higher incidence of prolonged neutropenia, serious medical complications, and death than patients with no risk factors. Some of the studies evaluating the role of CSFs in the treatment of febrile neutropenia (7–9) showed a reduced incidence of episodes of prolonged neutropenia or protracted hospitalization among the cytokine-treated patients. Subset analysis in two of the trials showed the greatest benefit in patients with profound neutropenia (absolute neutrophil count [ANC] $<100/\text{mm}^3$) and/or documented infection (7,10). These observations suggest that patients at higher risk of delayed hematologic recovery or with severe infection are probably the most likely to benefit from the therapeutic use of CSFs.

The purpose of this study was to evaluate in a prospective multicenter randomized clinical trial the efficacy and cost-

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effectiveness of G-CSF in the treatment of patients with solid tumors and high-risk febrile neutropenia.

PATIENTS AND METHODS

Patient Population

From January 1997 through March 1999, a total of 210 patients from five Spanish University Hospitals were enrolled on the study. Adult patients with solid tumors (including lymphomas) were eligible for enrollment if they presented with chemotherapy-induced neutropenic fever, defined as axillary temperature above 38 °C with an ANC below 500/mm³, and met at least one of the high-risk criteria. High-risk criteria were defined as follows: profound neutropenia (ANC <100/mm³), short latency from previous chemotherapy cycle (<10 days), sepsis or clinically documented infection at presentation, severe comorbidity, performance status greater than or equal to 3 [Eastern Cooperative Oncology Group —ECOG—scale (15)], prior inpatient status, and failure of ambulatory management of low-risk febrile neutropenia (persistence of fever and grade IV (16) neutropenia for >72 hours despite ambulatory treatment with quinolones). Severe comorbid conditions included the following: respiratory failure (partial pressure of oxygen <60 millimeters of mercury, adjusted for hyperventilation), congestive heart failure (New York Heart Association class III–IV), uncontrolled arrhythmia despite adequate therapy, renal failure (creatinine level greater than two times the upper limit of normal [ULN]), liver dysfunction (bilirubin level >2.5 times ULN or aspartate aminotransferase/alanine aminotransferase greater than four times the ULN), grade III–IV emesis (16), grade III–IV mucositis (16), grade III–IV diarrhea (16), symptomatic hypercalcemia, and uncontrolled bleeding. Patients were considered to be ineligible if they had a history of allergic reactions to the study drug (G-CSF) or to β -lactams or aminoglycosides, if they had been treated with hematopoietic growth factors in the preceding 7 days, if they were already receiving intravenous antibiotic therapy, if they were undergoing treatment with myeloablative chemotherapy that required progenitor-cell support, or if they were pregnant or breast-feeding. The study was approved by the Institutional Review Board of each hospital.

Study Design

All potentially eligible patients were evaluated by an internist and/or a medical oncologist at the emergency room or clinic. Baseline investigations included full medical history, physical examination, blood cell counts with differential leukocyte counts, blood and urine chemistries, chest radiograph, cultures of blood and urine, and investigation of other clinically suspicious sites. Once the diagnosis of febrile neutropenia was established and eligibility for study entry was confirmed, written informed consent was obtained from the patient. Subsequently, patients were admitted to the hospital and were randomly assigned by the consecutive drawing of sequentially numbered, opaque, sealed envelopes to receive or not G-CSF, in addition to broad-spectrum intravenous (i.v.) antibiotics. The allocation sequence was computer generated.

Empiric antibiotic treatment was immediately started with ceftazidime (2 g every 8 hours, i.v.) and amikacin (1 g every 24 hours, i.v., adjusted according to renal function). The addition of vancomycin (1 g every 12 hours as a 4-hour i.v. infusion, adjusted for renal function) was allowed if clinical evidence of catheter-related infection or suspicion of other gram-positive infection was present. For patients with dental or intra-abdominal infections or aspiration pneumonia, imipenem (500 mg every 6 hours, i.v.) was substituted for ceftazidime.

Antibiotic therapy was changed according to the following guidelines: 1) For relevant positive microbiologic findings, antibiotics were modified according to culture and antibiogram; 2) if new infectious foci became apparent after admission and if the patient remained febrile, antibiotics were modified accordingly; and 3) for patients with no new focality and persisting fever and neutropenia for 3 days, vancomycin was added. If fever and neutropenia persisted for 7 days, amphotericin B was added.

Treatment with antibiotics was maintained until the patient remained without fever for 2 consecutive days and had an ANC of 1000/mm³ or higher, provided that he or she had been on antibiotics for at least 5 days. Patients were to be discharged as soon as antibiotic therapy was discontinued, unless medically contraindicated. For patients randomly assigned to receive G-CSF, the growth factor was initiated within 12 hours of the diagnosis of neutropenic fever, at a dose of 5 μ g/kg per day given subcutaneously. Treatment with G-CSF was discontinued as soon as the ANC rose above 1000/mm³.

The overall cost per episode was calculated on the basis of the expenses concerning the treatment of each patient with fever and neutropenia, including days of hospital stay, antibiotics, G-CSF, blood transfusions, and total parenteral nutrition. The average cost of 1 hospital day at an Adult Oncology Unit of a Spanish National Public Health Service Hospital is 560 U.S. dollars (USD). The cost of a hospital stay included all activities concerning professional staffing (doctors, nurses, etc.) and materials (laboratory tests, diagnostic procedures, supportive patient care, etc.). The antibiotic drug prices used were wholesale prices. The cost of a 300- μ g G-CSF vial was 85 USD and of a 480- μ g vial was 110 USD. The cost of a blood transfusion was 433 USD for 2 U of packed red blood cells and 383 USD for 6 U of platelets. One day of total parenteral nutrition cost 110 USD.

Study End Points

The primary end point of the study was the duration of hospital stay. Secondary end points were days on antibiotic therapy, time to resolution of fever, number of days during which the neutrophil count was less than 500/mm³ and less than 1000/mm³, changes in antibiotic therapy, incidence of clinical complications, mortality rate, and costs.

Statistical Analysis

The median hospital stay of patients with febrile neutropenia and high-risk criteria treated without CSFs, according to our historic data, was 7 days (9,17). The number of episodes per branch necessary to detect a 2-day reduction in hospital stay, with a power of 80% ($\beta = 0.2$) and a significance level of 95% ($\alpha = 0.05$), was estimated to be 100. Assuming that approximately 5% of the patients would be ineligible, the total sample size of the study population was calculated to be 210. All eligible patients have been analyzed on an “intention-to-treat” basis.

Differences between the G-CSF and control groups regarding days of neutropenia, time to resolution of fever, days on antibiotic therapy, days of hospital stay, and costs were evaluated with the Mann–Whitney *U* test (18). The distribution of categorical variables among the two treatment groups was compared by the chi-square test (19,20) or Fisher’s exact test (21) when appropriate. The Cox proportional hazards model (22) was used for adjusted analysis of prognostic factors for number of days to resolution of neutropenia, antibiotic discontinuation, and hospital discharge. All *P* values were two-sided and were considered to be statistically significant at *P*<.05.

RESULTS

Two hundred ten patients were enrolled on the study from January 1997 through March 1999. Seven patients were ineligible because they did not meet the inclusion criteria: Two patients had an ANC above 500/mm³, and five patients did not meet any high-risk criteria (three did not have severe neutropenia and two did not have short latency from a prior chemotherapy cycle). Of 203 eligible patients, 104 were randomly assigned to receive antibiotic therapy with G-CSF and 99 were randomly assigned to receive antibiotic therapy alone (Fig. 1). Four patients randomly assigned to receive G-CSF did not complete the allocated treatment, since their treating physicians discontinued therapy with the growth factor earlier than required by the protocol. Six patients in the control group were given G-CSF at some stage of the episode, since their responsible clinicians judged their clinical situation to be sufficiently poor to start this treatment electively. All eligible patients were analyzed on an intent-to-treat basis. Patient characteristics are listed in Table 1. Potentially important prognostic variables were well balanced between both study groups.

Duration of Neutropenia, Antibiotic Treatment, and Hospitalization

The median number of days of G-CSF treatment for patients randomly assigned to receive this cytokine in addition to antibiotics was 3 days (range, 1–13 days), and 95% of these patients

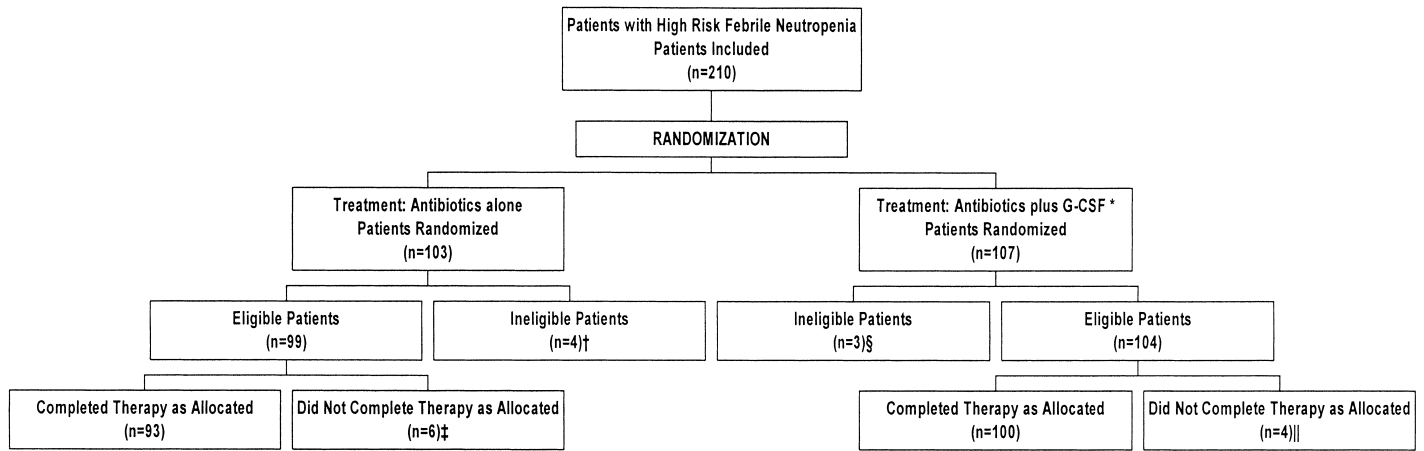


Fig. 1. Flow diagram of patients in the study. *G-CSF = granulocyte colony-stimulating factor. †One patient did not have grade IV neutropenia, and three did not meet the high-risk criteria (two patients did not have neutropenia $<100/\text{mm}^3$, and one did not have short latency from a prior chemotherapy cycle). ‡Six patients in the control group were given G-CSF at some stage of the episode, since their responsible clinicians judged their clinical situation to be sufficiently

unwell to electively start this treatment. §One patient did not have grade IV neutropenia, and two did not meet the high-risk criteria (one patient did not have neutropenia $<100/\text{mm}^3$, and one did not have short latency from a prior chemotherapy cycle). ||Four patients randomly assigned to receive G-CSF did not complete the allocated treatment, since their treating physicians discontinued therapy with the growth factor earlier than what it was required per the protocol.

required fewer than 6 days of G-CSF therapy. The median duration of grade IV neutropenia ($\text{ANC} < 500/\text{mm}^3$) was significantly shorter in patients treated with G-CSF (2 days) than in the control patients (3 days) ($P = .0004$) (Table 2). Recovery of the neutrophil count to $1000/\text{mm}^3$ occurred at a median of 3 versus 4 days for G-CSF and control patients, respectively ($P < .0001$) (Fig. 2). The duration of antibiotic therapy was statistically significantly reduced in the G-CSF-treated group compared with the control group (median, 5 days versus 6 days; $P = .013$). The median hospital stay was 5 days for patients treated with G-CSF, which was significantly shorter than the 7-day median hospital stay observed in the control group ($P = .015$) (Fig. 3). None of the study main end points were significantly different between sexes. G-CSF also reduced the incidence of prolonged antibiotic therapy or hospitalization. Forty-three patients (43%) in the control group required antibiotic treatment for at least 7 days versus 30 patients (29%) in the G-CSF group ($P = .04$). The number of patients with a hospital stay of 7 days or longer was 49 (49%) and 35 (34%) for the control and G-CSF groups, respectively ($P = .03$). Despite the resolution of the febrile neutropenia episode (end of antibiotic treatment), nine patients in the G-CSF group (9%) and 16 in the control group (16%) could not be discharged from the hospital ($P = .1$). The reasons for the prolonged hospitalization despite episode resolution included medical complications (six patients in the G-CSF group and 12 in the control group) and nonmedical reasons (three patients in the G-CSF arm and four in the control arm).

The beneficial impact of the treatment with G-CSF was further confirmed in a multivariate analysis (Table 3). The following variables were included in the model: profound neutropenia ($\text{ANC} < 100/\text{mm}^3$); short latency from previous chemotherapy cycle (< 10 days); sepsis or clinically documented infection at presentation; severe comorbidity; performance status greater than or equal to 3 (ECOG scale); prior inpatient status; failure of ambulatory management of low-risk febrile neutropenia; number of high-risk criteria per patient; age; number of days elapsed since last chemotherapy cycle; hemoglobin level, white blood cell (WBC) count, ANC, lymphocyte count, monocyte count, and platelet count at presentation; prior oral antibiotic therapy;

presence of a permanent indwelling catheter; number of prior chemotherapy regimens; number of prior febrile days; temperature greater than or equal to 39°C at presentation; and treatment arm (G-CSF versus control). The treatment arm remained a statistically significant predictive factor in the multivariate analysis for time to resolution of neutropenia, duration of antibiotic therapy, and length of hospital stay. Other independent prognostic factors in the Cox regression model for the above-mentioned study end points are summarized in Table 3.

Episode Outcome

The time to resolution of fever was similar in both study groups, with a median of 1 day for patients treated with G-CSF (25%–75% interquartile range, 1–3) and 1 day for patients in the control arm (25%–75% interquartile range, 1–3). The treatment was successful without the need for modifications in the antibiotic therapy in 50% of the episodes in the G-CSF group and in 52% of the episodes in the control group ($P = .78$) (Table 4). The need for antibiotic therapy modifications (G-CSF = 45% versus control = 43%; $P = .78$), vancomycin treatment (G-CSF = 32% versus control = 22%; $P = .23$), or amphotericin B treatment (G-CSF = 5% versus control = 2%; $P = .12$) was also not statistically significantly different between the study groups.

The success rate of either treatment was considerably higher in patients with fever of unknown origin than in patients with clinically or microbiologically documented infection, but no statistically significant differences in treatment outcome were found among treatment groups by episode classification (Table 4). The incidence of serious medical complications not present in the initial clinical evaluation was 10% (10 patients) in the G-CSF group and 17% (17 patients) in the control group ($P = .12$). Clinical deterioration because of the febrile neutropenia episode resulted in death in 10 of these patients, five in each study arm. The remaining case patients experienced nonfatal medical complications, including three episodes of congestive heart failure (two patients in the G-CSF group and two in the control group), four of respiratory failure (one patient in the G-CSF group and three in the control group), five of renal failure

Table 1. Patient characteristics by treatment arm* (all ranges are 25%–75% interquartile ranges)

Characteristic	Control† (n = 99)	G-CSF‡ (n = 104)
Median age, y (range)	61 (49–67)	59 (51–68)
Sex, female/male	51/48	44/60
Type of cancer (%)		
Breast cancer	38 (38)	32 (31)
Lung cancer	18 (18)	19 (18)
Other solid tumor	38 (38)	46 (44)
Lymphoma	5 (5)	7 (7)
High-risk criteria (%)		
Profound neutropenia	57 (57)	59 (57)
Early-onset neutropenia	35 (35)	37 (36)
Severe infection	26 (26)	37 (36)
Severe comorbidity	29 (29)	32 (31)
ECOG 3–4	24 (24)	23 (22)
Prior inpatient status	12 (12)	15 (15)
Failure of ambulatory management of low-risk febrile neutropenia	1 (1)	3 (3)
No. of high-risk criteria per patient (%)		
1	47 (47)	44 (43)
2	26 (26)	32 (31)
3	19 (19)	19 (19)
4	7 (7)	9 (9)
Type of episode (%)		
Fever of unknown origin	41 (41)	38 (37)
Clinically documented infection	35 (35)	48 (47)
Microbiologically documented infection	23 (23)	18 (17)
Permanent indwelling catheter (%)	13 (13)	14 (13)
Median WBC count at presentation (range)	730 (500–1142)	660 (400–1000)
Median ANC at presentation (range)	90 (34–210)	100 (50–190)
<100/mm ³ , No. (%)	56 (57)	51 (49)
100–500/mm ³ , No. (%)	42 (42)	53 (51)
Median lymphocyte count at presentation (range)	460 (220–700)	380 (190–750)
Median monocyte count at presentation (range)	100 (30–210)	77 (40–170)
Median No. of days since last cycle (range)	11 (9–13)	11 (8–13)
Median No. of previous cycles (range)	2 (1–3)	2 (1–4)
Median No. of previous regimens (range)	0 (0–1)	0 (0–1)

*WBC = white blood cell, ANC = absolute neutrophil count; ECOG = Eastern Cooperative Oncology Group performance status scale (15); G-CSF = granulocyte colony-stimulating factor.

†Control regimen consisted of ceftazidime and amikacin.

‡G-CSF regimen consisted of ceftazidime, amikacin, and G-CSF.

(two patients in the G-CSF group and three in the control group), one bowel obstruction (one patient in the control group), one acute episode of upper gastrointestinal bleeding (one patient in the control group), one deep-vein thrombosis and pulmonary embolism (one patient in the control group), and a syncope episode (one patient in the control group).

Cost Analysis

The median cost of a hospital stay was reduced by 17% (G-CSF group—median = 2875 USD, 95% confidence interval [CI] = 2645 to 3105; control group—median = 3450 USD, 95% CI = 3164 to 3736) ($P = .01$). The median costs of antibiotics were 480 USD and 565 USD for the G-CSF and

Table 2. Duration of neutropenia, antibiotic treatment, and hospital stay*

	Control† (n = 99)	G-CSF‡ (n = 104)	Two-sided <i>P</i>
Median days to ANC >500/mm ³ (95% CI)	3 (2 to 4)	2 (2 to 2)	.0004§
Median days to ANC >1000/mm ³ (95% CI)	4 (3 to 5)	3 (3 to 3)	<.0001§
Median days of antibiotic treatment (95% CI)	6 (5 to 7)	5 (5 to 5)	.013§
Median days of hospital stay (95% CI)	7 (6 to 8)	5 (5 to 5)	.015§
Duration of neutropenia <500/mm ³ at days after randomization, No. (%)			.005
1–3	52 (53)	77 (74)	
4–7	41 (41)	25 (24)	
>7	6 (6)	2 (2)	
Duration of neutropenia <1000/mm ³ at days after randomization, No. (%)			.0003
1–3	35 (35)	65 (63)	
4–7	56 (57)	37 (36)	
>7	8 (8)	2 (2)	
Antibiotic therapy ≥7 days, No. (%)	43 (43)	30 (29)	.04
Hospital stay ≥7 days, No. (%)	49 (49)	35 (34)	.03

*ANC = absolute neutrophil count; CI = confidence interval; G-CSF = granulocyte colony-stimulating factor.

†Control regimen consisted of ceftazidime and amikacin.

‡G-CSF regimen consisted of ceftazidime, amikacin, and G-CSF.

§Mann-Whitney *U* test.

||Chi-square test.

control arms, respectively ($P = .1$). The median cost of G-CSF was 255 USD. Other additional costs, including red blood cell and platelet transfusions (G-CSF group—median = 0 USD, mean = 165 USD; control group—median = 0 USD, mean = 152 USD; $P = .75$), and total parenteral nutrition (G-CSF group—median = 0 USD, mean = 46 USD; control group—median = 0 USD, mean = 30 USD; $P = .36$), were not statistically significantly different between the two treatment groups. Overall, the median total cost per patient admission was reduced by 11% (G-CSF group—median = 3960 USD, 95% CI = 3770 to 4150; control group—median = 4435 USD, 95% CI = 3933 to 4937; $P = .07$).

DISCUSSION

This study demonstrates that the use of G-CSF in the treatment of patients with solid tumors and chemotherapy-induced high-risk febrile neutropenia significantly improves the outcome of clinically relevant end points and is cost-effective. The addition of G-CSF to broad-spectrum antibiotic therapy resulted in a reduction of the median duration of grade IV neutropenia (33%; from 3 to 2 days), antibiotic treatment (17%; from 6 to 5 days), hospital stay (29%; from 7 to 5 days), and costs (11%; from 4435 to 3960 USD). The mortality rate was similar in both treatment arms; of interest, there was a trend toward a lower incidence of medical complications among G-CSF-treated patients (17% in the G-CSF group versus 10% in the control group). Therefore, G-CSF intervention allows this patient population to reduce safely the length of time spent in the hospital and the number of medical interventions at a lower cost. These ben-

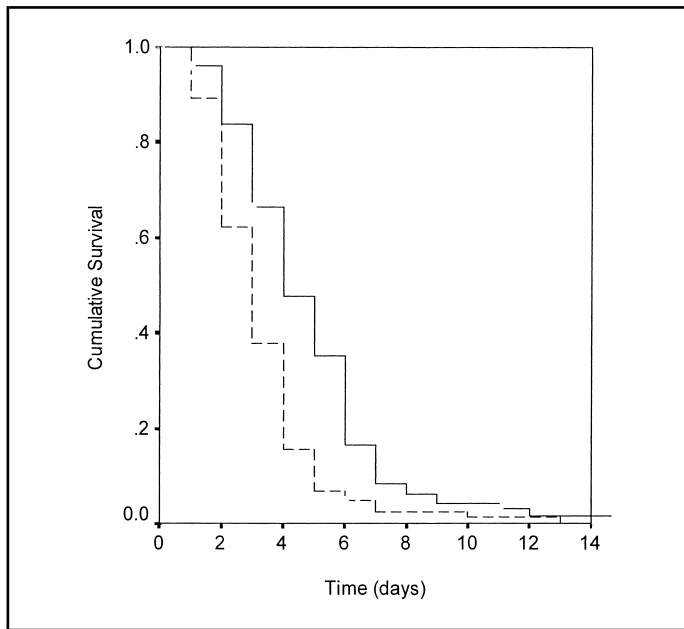


Fig. 2. Kaplan-Meier curves of time to ANC recovery greater than $1000/\text{mm}^3$ of G-CSF-treated patients (---) and of patients in the control arm (—) (log-rank test; $P = .0001$)*.

Days to ANC $>1000/\text{mm}^3$	% survival (95% CI)	No. of patients at risk
G-CSF group		
2	62 (52 to 72)	91
4	15 (8 to 22)	38
6	5 (1 to 9)	6
Control group		
2	84 (77 to 91)	94
4	47 (37 to 57)	64
6	17 (10 to 24)	33

*ANC = absolute neutrophil count, G-CSF = granulocyte colony-stimulating factor; CI = confidence interval.

efits are likely to have additional positive effects on subsequent quality-of-life measures and socioeconomic factors.

Several randomized studies (7–12) have attempted to address the role of hematopoietic CSFs in the treatment of febrile neutropenia, with somewhat conflicting results. In fact, the evidence-based American Society for Clinical Oncology recommendations for the use of hematopoietic CSFs in patients with neutropenia and fever state that “the available data do not clearly support the routine initiation of CSFs as adjuncts to antibiotic therapy for the majority of patients” (5,23). They indicate, however, that “the use of CSFs together with antibiotics may be reasonable in certain high-risk patients (pneumonia, hypotension. . .), even though the benefits of administration under these circumstances have not been definitively proved” (5,23). The lack of consistency in the results from previous CSF trials may be explained by several factors. First, the fact that patients with fever and neutropenia are a very heterogeneous population has not been taken into account in these trials to select the target population most likely to benefit from CSFs (7–12). Second, the criteria employed for CSF or antibiotic therapy duration or hospital discharge varied widely among the different studies (7–12). In addition, several of the studies were probably too small and had not enough power to detect the small, but still significant differences expected (8–11). Overall, all of the trials showed that

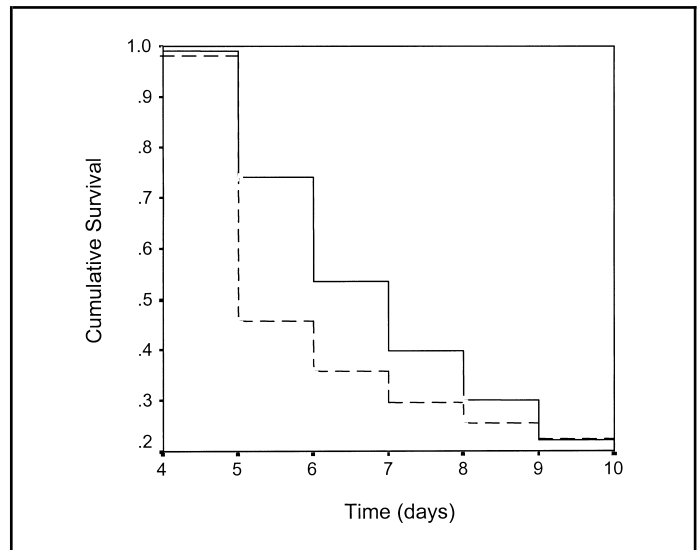


Fig. 3. Kaplan-Meier curves of length of hospital stay of G-CSF-treated patients (---) and of patients in the control arm (—) (log-rank test; $P = .015$)*.

Days to hospital discharge	% survival (95% CI)	No. of patients at risk
G-CSF group		
5	46 (36 to 55)	102
7	30 (22 to 38)	35
15	7 (1 to 13)	8
Control group		
5	73 (64 to 82)	96
7	39 (29 to 49)	48
15	14 (7 to 21)	12

*G-CSF = granulocyte colony-stimulating factor, CI = confidence interval.

the use of CSFs reduced the duration of neutropenia, but this benefit was not always associated with advantages in other more meaningful clinical end points (hospital stay, episode complications, cost, or mortality).

The eligibility criteria employed in our trial to select the target population were based on a medical risk predictive model described by Talcott et al. (13). This model considers a series of clinical variables that can be assessed within 24 hours of presentation in patients with fever and neutropenia and has been validated in 444 consecutive cancer patients from two different institutions (14). In these studies, serious medical complications occurred in 34% of the patients with risk factors, including prior inpatient status, serious independent comorbidity, or uncontrolled cancer, compared with a 5% incidence among the patients with no risk factors. The incidence of prolonged neutropenia (>7 days) was higher among the high-risk patients (61%) than among the low-risk patients (33%), and the risk of medical complications was smaller for patients whose neutropenia resolved in 7 days or fewer. Other independent prognostic factors for an increased risk of medical complications were short latency from chemotherapy to fever and neutropenia (<10 days) and age over 40 years. Multiple complications (17%) and death (10%) were common among patients in the high-risk groups, but they did not occur in the low-risk population.

The low incidence of severe infections or of protracted hematologic recovery among patients with uncomplicated febrile neutropenia and the demonstration of the safety and efficacy of early hospital discharge (24) or ambulatory management (17,25) in this patient population suggest a limited chance for CSF ben-

Table 3. Cox multivariate analysis for the three main study end points* (days were modeled as a continuous variable)

	Two-sided <i>P</i>
Days to ANC >500/mm ³	
WBC count at presentation	.01
Lymphocyte count at presentation	.04
Monocyte count at presentation	.03
Treatment arm (G-CSF versus control)	.003
Days of antibiotic treatment	
WBC count at presentation	.007
Lymphocyte count at presentation	.04
Permanent indwelling catheter	.01
Treatment arm (G-CSF versus control)	.05
Days of hospital stay	
WBC count at presentation	.002
Permanent indwelling catheter	.0006
Treatment arm (G-CSF versus control)	.01

*ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; ECOG = Eastern Cooperative Oncology Group performance status scale; WBC = white blood cell. Variables included in the model: profound neutropenia (ANC <100/mm³); short latency from previous chemotherapy cycle (<10 days); sepsis or clinically documented infection at presentation; severe comorbidity; ECOG performance status ≥3 (15); prior inpatient status; failure of ambulatory management of low-risk febrile neutropenia; number of high-risk criteria per patient; age; number of days elapsed since last chemotherapy cycle; hemoglobin level, WBC count, ANC, lymphocyte count, monocyte count, and platelet count at presentation; prior oral antibiotic therapy; presence of an indwelling catheter; number of prior chemotherapy regimens; number of prior febrile days; temperature ≥39°C; and treatment arm (G-CSF versus control). Only statistically significant variables are included in the table.

efit if these types of strategies are employed in low-risk patients. In our experience, most (58%) adult patients with solid tumors treated with conventional-dose chemotherapy belong to the low-risk category (17), which indicates that probably a high percentage of low-risk patients were included in the trials published to date (7–12). On the contrary, the observation in several trials that CSF therapy reduces the incidence of prolonged neutropenia (9), protracted antibiotic therapy (8), or hospitalization (7) suggests that patients at higher risk for a delayed hematologic recovery are the most likely to benefit from CSF therapy. The present study, which is the first randomized trial performed in patients with high-risk febrile neutropenia according to previously defined risk criteria that have been associated with prolonged hematologic recovery and/or with severe infection (13,14), has proven prospectively this hypothesis. It should be pointed out, nevertheless, that our patient population, in comparison with that of Talcott's studies, excluded patients with leukemia or those undergoing treatment with myeloablative chemotherapy that required progenitor-cell support. In addition, patients with lymphoma or those hospitalized previously are minimally represented. These patient populations are at higher risk for a delayed hematologic recovery and for subsequent complications (13,14). In fact, the incidence of serious medical complications (17%) and death (5%) in our study control arm, although greater than that observed in Talcott's low-risk group (5% and 0%, respectively), was considerably lower than that encountered among Talcott's high-risk patients (34% and 10%, respectively).

The current study was an open-label, non-placebo-controlled trial, since we did not have financial support to accomplish a double-blinded, placebo-controlled study design. Acknowledging this caveat and to minimize potential physicians' bias in the

Table 4. Treatment outcome

	Control (n = 99)	Granulocyte colony-stimulating factor (n = 104)	Two-sided <i>P</i>
Success (%)†	51 (52)	52 (50)	.78
Success with modification (%)†	43 (43)	47 (45)	
Failure‡	5 (5)	5 (5)	
Required vancomycin, No. (%)	22 (22)	33 (32)	.12
Required amphotericin, No. (%)	2 (2)	5 (5)	.23
Treatment outcome by episode classification			
Fever of unknown origin	41 (41)	38 (37)	.34
Success*	32/41 (78)	32/38 (84)	
Success with modification†	9/41 (22)	6/38 (16)	
Failure‡	0/41 (0)	0/38 (0)	
Clinically documented infection§	35 (35)	48 (47)	.78
Success*	12/35 (34)	16/48 (33)	
Success with modification†	20/35 (57)	30/48 (63)	
Failure‡	3/35 (9)	2/48 (4)	
Microbiologically documented infection	23 (23)	18 (17)	.41
Success*	7/23 (30)	4/18 (22)	
Success with modification†	13/23 (57)	11/18 (61)	
Failure‡	2/23 (9)	3/18 (17)	

*Episode resolution with no modification of the initial empiric antibiotic therapy (ceftazidime + amikacin).

†Episode resolution with modification of the initial antibiotic therapy.

‡Death from the febrile neutropenia episode.

§Included: respiratory infection, 41 patients; ear, nose, and throat infection, 23; gastrointestinal infection, 12; abdominal infection, five; perianal infection, four; urinary infection, four; cutaneous infection, 14; and phlebitis, three.

||Included the following organisms isolated from: blood—*Staphylococcus aureus*, three patients; *Staphylococcus epidermidis*, two; *Streptococcus β-hemolyticum*, two; *Streptococcus viridans*, one; *Enterococcus faecalis*, two; *Propionibacterium*, one; *Escherichia coli*, five; *Enterobacter*, one; *Pseudomonas*, eight; *Salmonella*, one; *Klebsiella*, one; *Pasteurella*, one; *Candida tropicalis*, one; urine—*Escherichia coli*, six; *Enterococcus faecalis*, one; *Acinetobacter*, one; *Pseudomonas*, one; Pleural effusion—*Nocardia*, one; Subcutaneous Abscess—*Staphylococcus aureus*, one; *Pseudomonas aureginosa*, one; oropharynx mucosa—*Pseudomonas* and *Candida albicans*, one.

assessment of outcome since the treatment group was known, CSF therapy duration, antibiotic discontinuation, and hospital discharge decisions were all based on clear-cut objective criteria (temperature, ANC, and number of days on therapy). Treatment with antibiotics was maintained until the patient remained without fever for 2 consecutive days and had an ANC of 1000/mm³ or higher, provided that he or she had been on antibiotics for at least 5 days. Patients were to be discharged as soon as antibiotic therapy was discontinued, unless medically contraindicated. These criteria have been used for more than a decade by our group and have proved to be safe and not associated with complications following patient discharge (9,17); they are among the least stringent reported in the literature. The duration of antibiotic treatment or hospital stay was, indeed, remarkably shorter in our trial than in most other published studies (7–12,26,27), even though some of them were performed in low-risk populations (26,27). This indicates that it is unlikely that the mentioned discharge rules may have substantially extended the duration of hospitalization in a substantial number of patients. In any case, more conservative policies for antibiotic treatment duration or hospital discharge are most likely to diminish the clinical impact of an earlier neutrophil recovery. Therefore, if the use of these rules mandated by the protocol were to have had any influence on the study outcome, this would have tended to minimize the benefit of G-CSF therapy. Indeed, the median duration of hospitalization was 5 days among the G-CSF-treated patients, the minimum required per protocol. One could argue that some of these patients may have been discharged earlier had this decision been based on resolution of fever and return of neutrophil count alone.

Besides treatment with G-CSF, other factors, such as WBC, lymphocyte, and monocyte counts at presentation, were found in our trial to have a substantial impact on time to resolution of grade IV neutropenia. No CSF therapy, a low WBC count at presentation, and the presence of an indwelling catheter were also independently associated with a longer hospital stay. Of interest, none of the different risk criteria employed for patient selection, whether associated with protracted hematologic recovery or with severe infection, were found to have an independent prognostic value in terms of neutropenia duration, time on antibiotics, or hospitalization.

The cost of CSFs combined with their current wide-scale application has raised some economic concern among caregivers and payers. The main issue to be defined in the febrile neutropenia setting is the threshold risk at which the added cost of the growth factor would be offset by the reduction in cost associated with a decrease in the duration of hospitalization and/or resources utilized. In the high-risk population included in this study, which represents about 30%–40% of the solid tumor patients with fever and neutropenia, G-CSF therapy significantly reduced the cost of hospital stay, which is the major economic-driving factor of the episode cost estimate. We believe that the observed 17% reduction in the median hospital cost per patient in the G-CSF group could have been greater if this had been calculated from the actual resources utilized by each individual patient, since G-CSF reduced the most expensive episodes, such as those associated with long hospital stays or with medical complications. Unfortunately, the hospitals of the Spanish National Public Health Service Program do not provide data on individual expenses per specific patient admission but rather average day-cost estimates according to type and complexity of

admission episode, type of admission unit, and length of hospital stay. In addition, the modest decrease of 475 USD in median overall cost per patient admission would be of a greater magnitude in settings where the febrile neutropenia costs are higher [e.g., 7736 USD in the study by Rubenstein et al. (28) or 8836 USD in the study by Cantor et al. (29), in contrast with 4435 USD in the present series]. Finally, our cost estimates did not include direct costs incurred by the patient and family while receiving medical care (transportation, etc.) or indirect costs related to the loss of income for days of work lost by patients and relatives due to hospitalization or early death.

The role of CSFs in other settings of febrile neutropenia remains undefined. In our opinion, G-CSF treatment has a limited chance to be cost-effective in low-risk patients, in whom alternative management approaches (early discharge and/or outpatient care) are safe and inexpensive (17,24,25). On the other hand, in very high-risk populations, such as leukemia patients or patients hospitalized previously or undergoing myeloablative chemotherapy with stem cell support, who were excluded or minimally represented in our trial, it is unlikely that G-CSF therapy could decrease costs, since early hospital discharge is rarely feasible. Whether this cytokine effectively reduces the morbidity and mortality of this last subset of patients also remains uncertain. Therefore, it is probably an intermediate- to high-risk population, such as that defined in our study, that is the most likely to benefit from cytokine therapy. Our study was not designed for or powered enough to do further subgroup analysis. Future studies should aim to define better whether different subsets of patients with different high-risk criteria may benefit more than others from this intervention.

In conclusion, the study presented here demonstrates that the use of G-CSF, in addition to antibiotics, in the treatment of an appropriately chosen, high-risk subset of patients with chemotherapy-induced febrile neutropenia accelerates neutrophil recovery, shortens antibiotic therapy and hospitalization, and may reduce costs. Thus, G-CSF should be used as part of the standard therapy in the management of febrile neutropenic patients with solid tumors meeting these risk criteria.

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